REMARKS

Claims 81-91 are pending. Claims 81-86 have been amended to more particularly point out what applicants regard as the invention. Support for these amendments may be found in the specification, *inter alia*, at pages 76 and 77 and in Figure 8 and previous Figure 12, corresponding to new Table 6. Applicants submit that these amendments raise no issue of new matter. Thus, claims 81-91 are now pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the June 17, 2003 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

Formalities

The Examiner stated that the drawings in this application have been objected to by the Draftsperson under 37 C.F.R. §1.84 or §1.152 and that applicants are required to submit a proposed drawing correction in reply to this office action.

In response, applicants submit proposed drawing corrections for Figures 1, 2, and 7-10, as shown in the attached sheets. Applicants note that Figures 11-14 have been deleted and corresponding Tables 5-8 have been inserted into the specification.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 81-91 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner stated that "the cited claims do not describe distinguishing identifying characteristics [of the claimed

antibodies]" and further that "[t]he instant antibodies are not identified by name or by binding affinity [in the claims]. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims." (parentheticals omitted).

Applicants understand the Examiner's remarks to indicate that the recitation in the claims of the relative binding affinities of the antibodies for hCG isoforms would satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Accordingly, applicants have amended claims 81 and 82 to recite the binding affinities of the antibodies of the claimed methods. Support for this amendment is found in the specification at pages 76 and 77 and in Figure 8 and new Table 6, corresponding to previous Figure 12.

In view of the above remarks, applicants maintain that claims 81-91 satisfy the requirements of U.S.C. §112, first paragraph, and respectfully request that the Examiner withdraw her rejection thereof.

Obviousness-Type Double Patenting Rejection

The Examiner rejected claims 81-91 as allegedly unpatentable over claims 1-12 of U.S. Patent No. 6,500,627 in view of El-Ahmady under the judicially created doctrine of obviousness-type double patenting. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because the claims employ the same methods steps while utilizing the same reagents. The Examiner alleges that the preambles reciting "A method of predicting pregnancy outcome" and "A method of detecting gestational trophoblast malignancy" encompass the same subject matter. In support, the Examiner cites the El-Ahmady (1996) abstract.

In response to the Examiner's rejection, applicants respectfully maintain their traversal for the reasons set forth in their

Amendments of July 17, 2001 and April 10,2002 and for the additional reasons set forth below.

El-Ahmady teaches the clinical value of the beta core fragment of hCG in patients with urogenital disorders. El-Ahmady concludes, in relevant part, that "[as] a tumor marker, [the beta core fragment] was more sensitive and more specific in bladder than in gynecological cancer." Applicants maintain that, contrary to the Examiner's interpretation, El-Ahmady teaches away from the clinical usefulness of the beta core fragment in detecting gynecological cancer. Applicants further point out that nothing in El-Ahmady teaches or suggests the clinical usefulness of the EPMI-hCG of the instant invention.

In view of these remarks, applicants maintain that new claims 81-91 are patentable over claims 1-12 of U.S. Patent No. 6,500,627.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 81-91 under 35 U.S.C. §103(a) as allegedly unpatentable over Ellish et al. (1996) in view of Krichevsky et al. (U.S. Patent No. 6,339,143) and further in view of Price et al. (1996).

In response to the Examiner's rejection, applicants respectfully traverse.

Ellish describes a population-based prospective study of early pregnancy loss in New York State. To detect an early pregnancy, Ellish utilized three antibodies to hCG, namely, B109, B204, and B108. Contrary to the Examiner's assertion, Ellish does not teach the B207 antibody. Importantly, Ellish does not distinguish among the hCG isoforms detected by the various antibodies, nor does Ellish teach the EPMI-hCG isoform that is detected by the B152 antibody, which detection and its clinical significance form the basis of the present invention.

Krichevsky et al. teach methods and antibodies to measure hCG. However, Krichevsky does not teach the method of the instant invention, namely a method for detecting trophoblast malignancy using a ratio of EPMI-hCG to intact hCG. Notably, Krichevsky does not describe this ratio at all. The ratio used by Krichevsky for the detection of Down's syndrome is the ratio of the free beta subunit to intact hCG.

Finally, Price teaches that Asian women have an increased risk of thyrotoxicosis resulting from excessive thyroidal stimulation by hCG during pregnancy.

The present invention is based upon the discovery that persistent high levels of EPMI-hCG may indicate a form of cancer called gestational trophoblast malignancy. The instant methods comprise an immunoassay to detect the level of EPMI-hCG relative to that of intact hCG in a sample from a subject.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest every element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Applicant maintains that the cited references fail to support a *prima facie* case of obviousness for the reasons set forth below.

First, the cited references, when combined, do not teach each and every element of the claimed invention. None of the references cited by the Examiner teach either the EPMI-hCG isoform of hCG recognized by the B152 antibody or its clinical significance in the diagnosis of trophoblast malignancy. Nor do any of the cited references teach the use of the B152 antibody in a method to detect trophoblast malignancy.

The closest prior art cited by the Examiner is Krichevsky, which teaches a method for detecting a malignant tumor by determining the amount of nicked hCG in a sample. Notably, nicked hCG is a different analyte than the EPMI-hCG measured in the instant method. Contrary to the Examiner's statement, the B152 antibody does not preferrentially bind to nicked hCG over the non-nicked form (see page 77, lines 4-8 and new Table 6, corresponding to previous Figure 12, in the specification). Therefore, the B152 antibody could not be used in the method of Krichevsky.

Instead, B152 is highly selective for the C5 choriocarcinoma-derived isoform of hCG, which is similar to EPMI-hCG, as taught in the instant specification at page 40, lines 24-26 and in new Table 6. The usefulness of the B152 antibody in detecting the choriocarcinoma-derived isoform of hCG is not taught or suggested in any of the cited references.

Thus, the combined references fail to teach or suggest every element of the claimed invention. In particular, the cited references do not teach or suggest either (1) the immunodectection of EPMI-hCG; (2) a ratio of EPMI-hCG to intact hCG; or (3) the detection of trophoblast malignancy based on a ratio of EPMI-hCG to intact hCG.

In view of these remarks, applicants maintain that claims 81-91 satisfy the provisions of 35 U.S.C. §103(a) and respectfully request that the Examiner withdraw her rejection thereof.

Summary

In view of the remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

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